

### **Remarks**

Claims 45-49 are pending in this application and stand rejected under 35 USC §101/112 for alleged lack of utility and under 35 USC §112, second paragraph. Applicants respectfully traverse these rejections.

### **Priority**

The Examiner asserts that the disclosures of the International application PCT/US99/30095 filed December 16, 1999, and US provisional application 60/113296, filed December 22, 1998 do not provide utility for the same reasons that utility is denied for the present application.

As will be apparent from the discussions below under utility, Applicants submit that the results of the gene amplification assay provided in these disclosures render specific and substantial asserted utility for the instant claims reciting a method for diagnosing lung or colon cancer using antibodies to PRO343. Thus, Applicants believe that they are entitled to at the priority of **December 22, 1998**.

### **Claim Rejections – 35 USC § 101/112**

Claims 45-49 are rejected under 35 USC §101, first paragraph, allegedly for lack of utility. The Examiner asserts that "no correlation was established between the polypeptides of SEQ ID NO: 263 and lung or colon cancer or any other disease". The Examiner adds that the art allegedly does not recognize that protein levels are increased when gene amplification occurs. While acknowledging that Pennica *et al.* only represents one class of proteins, the Examiner cites further references like Haynes and Konopka to conclude that "it does not necessarily follow that a increase in gene copy number results in increased gene expression or protein expression." From this, the Examiner concludes that the PRO343 polypeptide and its antibodies lack specific or substantial utility. For the same reasons, the Examiner also concludes that one of skill in the art

would not know how to use the claimed antibodies in a method for diagnosing lung or colon cancers.

Applicants respectfully traverse these rejections and outline the reasons below for Applicants' assertion that the gene amplification assay provides adequate support for patentable utility of the antibodies directed to PRO343 polypeptides.

### **Utility Guidelines**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P. 2107 II (B) (1)

gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

### Arguments

#### Applicants maintain that a *prima facie* case of lack of utility has not been made

The Examiner bases the assertion, that "increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression" on exemplary literature articles like Haynes and Konopka *et al.*, and hence concludes that the antibodies directed to the PRO343 polypeptides lack utility.

The Examiner cites the Haynes *et al.* reference to establish that even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also

amplified. The Examiner adds that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*

Finally, the Examiner cites Konopka *et al.* to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results of the *abl* gene alone. Thus, the teachings of Konopka are not directed towards genes in general, but to a single gene, and thus, its teachings have been misrepresented in this rejection.

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, as observed for the *abl* gene, is typical. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.* (cited previously), a correlation between DNA amplification: polypeptide

over-expression was observed in the case of *WISP-1* and similarly, in Haynes *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

Applicants further submit that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack *et al.*, who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that gene amplification correspondingly increases mRNA expression, in general.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified

approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm, which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art exemplified by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, and the Polakis declaration overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO343 gene, that the PRO343 protein is concomitantly overexpressed. Thus, Applicants submit that the antibodies to the PRO343 protein also have utility in the diagnosis of cancer and thus, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO343, which Applicants submit is not true, Applicants maintain that polypeptides encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. Once again, Applicants draw the Examiner's attention to a Declaration by Avi Ashkenazi, Ph.D. that was previously submitted which explains that:

even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or

over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Therefore, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO343 polypeptide and its antibodies, for example, in detecting over-expression or absence of expression of PRO343. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed antibodies in a method for the diagnosis of lung or colon cancer. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

#### **Claim Rejections – 35 USC §112, second paragraph**

Claims 45-49 are rejected under 35 USC §112, second paragraph, allegedly for being indefinite in reciting the term "specifically." Applicants respectfully traverse this rejection.

Applicants submit that the art-recognized meaning of "specifically" binding is well understood in the art to mean that the antibody in question specifically binds to a particular antigen while not significantly cross-reacting with another antigen. Any skilled person in the art would know what the scope of the claimed invention is as recited in the claims. Therefore, Applicants respectfully request that this rejection to claims be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

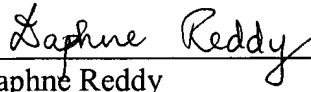
Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C49).



Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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